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Estimating the alcohol–breast cancer association: a comparison of diet diaries, FFQs and combined measurements

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Abstract The alcohol–breast cancer association has been established using alcohol intake measurements from Food Frequency Questionnaires (FFQ). For some nutrients diet diary measurements are more highly correlated with true intake compared with FFQ measurements, but it is unknown whether this is true for alcohol. A case–control study (656 breast cancer cases, 1905 matched controls) was sampled from four cohorts in the UK Dietary Cohort Consortium. Alcohol intake was measured prospectively using FFQs and 4- or 7-day diet diaries. Both relied on fixed portion sizes allocated to given beverage types, but those used to obtain FFQ measurements were lower. FFQ measurements were therefore on average lower and to enable fair comparison the FFQ was "calibrated" using diet diary portion sizes. Diet diaries gave more zero measurements, demonstrating the challenge of distinguishing never-from episodic-consumers using short term instruments. To use all information, two combined measurements were calculated. The first is an average of the two measurements with special treatment of zeros. The second is the expected true intake given both measurements, calculated using a measurement error model. After confounder adjustment the odds ratio (OR) per 10 g/day of alcohol intake was 1.05 (95 % CI 0.98, 1.13) using diet diaries, and 1.13 (1.02, 1.24) using FFQs. The calibrated FFQ measurement and combined measurements 1 and 2 gave ORs 1.10 (1.03, 1.18), 1.09 (1.01, 1.18), 1.09 (0.99,1.20), respectively. The association was modified by HRT use, being stronger among users versus non-users. In summary, using an alcohol measurement from a diet diary at one time point gave attenuated associations compared with FFQ.

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Introduction

Breast cancer is the most common type of cancer in women worldwide [1] and several large studies and meta-analyses have concluded that increased breast cancer risk is associated with higher alcohol intake [2–12]. Breast cancer has been added to the list of cancers for which there is convincing evidence of a causal relationship with alcohol consumption by the International Agency for Research on Cancer (IARC) [13] and World Cancer Research Fund/ American Institute for Cancer Research 2007 report [11].

The exposure of interest in nutritional epidemiology is typically the long term average or 'usual' daily intake of a given nutrient or food group. It is not feasible to observe true exposure and studies rely on self-reported measures of intake. Food frequency questionnaires (FFQs) are the most widely used dietary assessment instrument in large observational studies of adults; these are structured questionnaires listing varying numbers of foods, and individuals report how often they consume each item from a range of frequency options, considering their intake over a period such as the previous several months or year [14]. Limitations of FFQs are that they are restricted to listed food items and most often do not record detailed portion size information. Other dietary assessment instruments include 24-h recalls, which ask individuals to report their intake on the previous day and are often conducted by interview, and diet diaries, on which individuals record all their intake over a period of several days. These instruments provide more detailed information than FFQs but provide a "snapshot" of intake over a short time period which is assumed to reflect a habitual pattern. Because of their expense, 24-h recalls and diet diaries have been used mainly as validation tools in large cohorts rather than as the main instrument. Error in self-reported measurements of dietary intake is a major problem in nutritional epidemiology, resulting in biased, typically attenuated, estimated diet-disease associations [15]. Some studies have quantified the error in FFQ and diet diary or 24-h recall measurements by comparison with objective recovery biomarkers, which provide unbiased measures of true intake but of which there are very few. Validation studies using recovery biomarkers for protein, potassium and total energy intake have found diet diary or 24-h recall measurements to be more highly correlated with the biomarkers, and with the underlying but unobserved 'true intake' using measurement error modelling, compared with FFQs [16–18]. For nutrients for which there is no recovery biomarker, results from using FFQs and diet diaries have been compared in case–control studies within cohorts. A study of fibre intake and colorectal cancer in the UK Dietary Cohort Consortium found a significant inverse association using diet diary data but not using FFQ data [19]. Two studies have observed significant positive associations between fat intake and breast cancer using diet diary but not FFQ data [20, 21], though a recent study found no association using either instrument [22].

What is not yet known is whether diet diaries provide a less error prone measure of intake for 'episodically consumed' items, such as alcoholic drinks, compared with FFQs, in the absence of recovery biomarkers. Episodically consumed foods are those which are not consumed every day by many individuals, and another example is fish; this is in contrast to nutrients such as fat which will be consumed daily because of their dispersion among many foods. Episodically consumed items may not be recorded in short term records such as diet diaries. In the case of alcohol there is also the issue that some individuals are never-consumers. Where zero intake is recorded in a diet diary from one time point, it is not possible to distinguish between episodic- and never-consumers. FFQs do not, at least in theory, suffer from this issue. On the other hand, diet diaries collect much more detailed information on alcohol intake for individuals reporting non-zero intake compared with FFQs.

In this paper we compare, for the first time, the association between alcohol intake and breast cancer using data from both FFQs and 4- or 7-day diet diaries obtained in the UK Dietary Cohort Consortium, which has pooled data from matched case–control studies of breast cancer sampled within four UK cohort studies from which nutritional data were available from both diet diaries and FFQs. Measurements of alcohol intake from both instruments rely on fixed portion sizes and to deal with this, the FFQ was "calibrated" using diet diary portion sizes. We also propose two measurements which combine FFQ and diet diary information. It has been suggested that the alcohol–breast cancer association may be modified by hormone replacement therapy (HRT) use, menopausal status, and folate intake. Interactions between alcohol intake and these variables are also investigated.

Methods

Study population

Individual participant data were pooled from matched case–control studies of breast cancer sampled from four studies in the UK Dietary Cohort Consortium [19]: EPIC-Norfolk, EPIC-Oxford, the UK Women's Cohort Study (UKWCS)

Table 1 Summary of studies in the UK Dietary Cohort Consortium case–control study of breast cancer

Study	Number of cases/controls	Age range at diary completion	Mean age at diagnosis	Date range of diary completion	Last date of follow-up
EPIC-Norfolk	353/1252	40–78	65.0 (9.0)	Feb 1993–Apr 98	31 March 2010
EPIC-Oxford	194/194	23–88	56.9 (11.0)	Feb 1993–Apr 99	31 Dec 2006
UKWCS	41/196	40–75	59.1 (9.4)	May 1999–Feb 02	31 March 2006
Whitehall II	68/263	39–61	58.3 (6.5)	Sep 1991–Apr 93	30 Sept 2005

and Whitehall II. The individual cohorts and methods of dietary assessment have been described elsewhere [23–28]. The MRC National Survey of Health and Development is also part of the UK Dietary Cohort Consortium, but was excluded from this analysis because it provided diet diary but not FFQ measurements [29]. Each cohort collected dietary information using 7-day (EPIC-Norfolk, EPIC-Oxford, Whitehall II) or 4-day (UKWCS) diet diaries completed on consecutive days at recruitment to the study. FFQs were administered just before or concurrently with the diaries. Anthropometric measurements and lifestyle factors were collected by trained researchers or in questionnaires administered prior to or concurrently with the dietary assessments. The studies are summarised in Table 1.

Selection of cases and controls

Breast cancer cases were women free of cancer (except non-melanoma skin cancer) at the date of diary commencement and who developed breast cancer at least 6 months after that date, but before the end of the study period (Table 1). Incident cases (International Statistical Classification of Diseases and Related Health Problems 9th and 10th revision: codes 174, C50) were ascertained by record linkage with local cancer registries and the UK Office for National Statistics.

Within studies, each case was matched to up to five controls based on age at recruitment (±3 years) and date of diary completion (±3 months). Controls were required to be free of all cancer (except non-melanoma skin cancer) at the date of diary commencement and free of breast cancer at the end of follow-up. In all studies apart from UKWCS, controls were required to have at least as much follow-up time as their case, with the exception of a small number of cases in EPIC-Norfolk where this condition was relaxed to obtain sufficient controls. The data from EPIC-Oxford were restricted to women who were non-users of HRT, because the data originated from an existing case–control sample.

A small number of individuals did not have FFQ measurements and were excluded (46 EPIC-Norfolk, 3 UKWCS, 8 Whitehall II). This investigation is based on 656 breast cancer cases and 1905 matched controls.

Dietary assessment

FFQs are structured questionnaires designed to measure 'habitual' intake and completers were asked to consider their dietary intake over the past year. EPIC-Norfolk and EPIC-Oxford used the same FFQ while those used in Whitehall II and UKWCS differed slightly. The FFQs used by EPIC-Norfolk, EPIC-Oxford and Whitehall II asked individuals to report one of 9 frequencies of intake for each food item: never or less than one/month, 1–3/month, once a week, 2–4/week, 5–6/week, once a day, 2–3/day, 4–5/day, 6+/day. UKWCS divided the lowest category of consumption into "never" and "less than one/month", and the other categories were as above. For each food item a portion size is stated on the questionnaire; these are mostly non-specific (e.g. a 'medium serving'). To obtain continuous measurements of food intakes the FFQ software program assigned a portion size (e.g. in grams) to each item, which is combined with the frequency of intake to give a measurement of intake. In EPIC-Norfolk the following frequencies of intake per day were assigned to the 9 categories of intake detailed above: 0, 1/14, 1/7, 3/7, 5.5/7, 1, 2.5, 4.5, 6. The frequencies used for each response category differed only slightly in other studies.

In the diet diary participants were asked to record in detail all the foods and beverages they consumed at designated times throughout the day, usually as prompted by time slots (e.g. breakfast, mid-morning, evening meal). Descriptions of how to report portion size were provided. Participants were not specifically instructed to weigh or measure their items, though for some items it was suggested that amounts could be reported by volume. A series of photographs were also provided showing small, medium and large portions of a range of commonly eaten foods.

Diet diaries were coded to give nutrient and food group intakes using the Data into Nutrients for Epidemiological Research (DINER) program developed in EPIC-Norfolk [30], with the exception of UKWCS food diaries which were pre-coded using the Diet And Nutrition Tool for Evaluation (DANTE) program [31]. We compared 100 food diaries coded under both programs and found good agreement for most nutrients, though the geometric mean intake of alcohol from DINER was 7% higher (95 % CI = 3–11 %) than from DANTE.

Assessment of alcohol intake

The EPIC-Norfolk and EPIC-Oxford FFQ included questions on consumption of four types of alcoholic beverage: "wine (glass)", "beer, lager or cider (half pint)", "port, sherry, vermouth, liqueurs (glass), "spirits, e.g. gin, brandy, whisky, vodka (single)". The UKWCS FFQ separated beer/lager from cider and the Whitehall II FFQ

Table 2 Summary of portion sizes used in FFQ and diet diary measurement calculations

Study centre	Program-assigned portion size (ml)	Assigned alcohol per 100 ml (g)
A. FFQ: Program-assigned portion size and amount of alcohol per 100 ml for each alcoholic beverage type		
EPIC-Norfolk, EPIC-Oxford		
Wine	125	8.7
Beer/lager/cider	288	3.93
Spirits	23	31.7
Fortified wine/liqueurs	50	13.15
Whitehall II		
Wine	125	9.1
Beer/lager/cider	287	2.5
Spirits	23	31.7
Fortified wine	48	15.9
Liqueurs	25	18.66
WKWCS		
Wine	125	9.25
Beer/lager/cider	287	3.08
Spirits	23	31.7
Fortified wine/liqueurs	40	16.65

Diet Diary program	Program-assigned non-specific portion size (ml)	Mean (SD) alcohol per 100 ml (g)	Average portion size (ml)[a]	Average alcohol (g) per average portion size
B. Diet diary: Program-assigned non-specific portion size and average amount of alcohol per 100 ml for each alcoholic beverage type. Average portion size and corresponding average amount of alcohol per average portion size were used to obtain the calibrated FFQ measurements				
DINER (EPIC-Norfolk, EPIC-Oxford, Whitehall II)				
Wine	175	8.76 (1.53)	173.4	15.2
Beer/lager	284.5	3.31 (0.95)	284.5[b]	9.4[c]
Cider	284.5	4.23 (1.74)	284.5[b]	12.0[c]
Spirits	37.5	30.53 (1.04)	42.6	13.0
Fortified wine	63 (sherry)	14.63 (1.36)	51.9	7.6[d]
	75 (other fortified wine)			
Liqueurs	37.5	22.23 (7.63)	42.3	9.5[d]
DANTE (UKWCS)				
Wine	125	9.32 (0.58)	125	11.7
Beer/lager	287	3.19 (1.18)	287[b]	9.0
Cider	287	3.76 (0.05)	287[b]	10.7
Spirits	23	30.88 (0.99)	23	7.0
Fortified wine	50	14.65 (1.52)	50	7.3[d]
Liqueurs	25	21.50 (6.16)	25	5.5[d]

[a] It was not possible to calculate average portion size using DANTE data. This was because the available data gave the total amount consumed in ml and corresponding amount of alcohol per day and by beverage type, but was not in general broken down into individual drinks as in DINER data. Assigned portion sizes in these data were strongly dominated by the non-specific portion sizes

[b] It was not necessary to calculate an average portion size for beer and cider because a half pint measure was specified on the FFQ

[c] The average proportion of beer plus cider intake which was beer was 0.82

[d] The average proportion of fortified wine and liqueur intake which was fortified wine was 0.84 in both DINER and DANTE data

separated liqueurs from fortified wine. The portion sizes assigned to each beverage type [in millilitres (ml)] are shown in Table 2A alongside the strength assumed for each beverage type (in grams of alcohol per 100 ml). Portion sizes and assumed strength differed somewhat across studies and we did not standardise them; these figures were used in conjunction with the reported frequencies of intake to calculate average alcohol amount per day for each beverage. These were summed across beverage types to give average daily total alcohol intake in g/day.

In the diet diary data used for this study, alcoholic drinks were divided into six categories: wine, beer/lager, cider, fortified wine, liqueurs, spirits. In the diet diaries, measured portions (e.g. in ml) were rarely reported and instead descriptive terms were used (e.g. 'small glass', 'measure'), with the exception of beer, where pints, or parts thereof, were reported. The descriptive terms were used to assign a portion in DINER (e.g. 'wine glass'), and where it was reported the relative size, i.e. small (S), medium (M) or large (L); or, where not specified, a non-specific (n.s.) portion size was assigned. Non-specific portion sizes were typically taken to be a 'medium' portion. Many individuals did not give detail about the relative portion size. For example in the DINER data 86 % of wine drinkers always reported wine in a wine glass, of which 84 % were assigned a non-specific wine glass on every occasion this item was reported in the diet diary. The following portions appeared in the data: bottle (S, n.s.), can (S, L, n.s.), vending size cup (n.s.), dash, dessertspoon, glass (S, M, L, n.s.), sherry glass (S, M, L, n.s.), tumbler (S, M, L, n.s.), wine glass (S, M, L, n.s.), mug, sprinkle, tablespoon, teaspoon, alcohol measure (at home, in the pub, n.s.), mouthful, unknown portion. The DANTE program has a much less extensive range of built-in portions, and non-specific portion sizes were assigned in many cases. For example, it was not possible to tell whether a recorded portion of 125 ml of wine was assigned because the glass size was not specified or because the individual reported intake in millilitres. In both DINER and DANTE an amount in millilitres was assigned to each portion and the corresponding amount of alcohol was calculated using information about the drink consumed. Total alcohol consumed over the course of the diet diary was divided by the number of days over which it was completed to estimate average daily alcohol intake in g/day. The non-specific portion sizes and average amounts of alcohol assigned per 100 ml for each beverage type, under each data-entry program (DINER, DANTE), are summarised in Table 2B.

For a given beverage the non-specific portion size assigned in the DINER program tended to be larger than the FFQ portion size, with the exception of 'beer', the only beverage for which a measured portion size was referred to on the FFQ (half pint), while this was not in general the case in the DANTE program. To enable a fair comparison between the two dietary assessment instruments, we "calibrated" the FFQ measurements using portion sizes derived from diet diary measurements. This was done separately for each beverage type listed on the FFQ. For diet diaries coded using DINER, we calculated the average diet diary portion size for each beverage type (excluding measures assumed to refer to alcohol used in cooking, such as 'dash') and the corresponding average amount of alcohol (drink strength). For diet diaries coded using DANTE the available data was such that it was not possible to calculate average portion sizes, so the average amount of alcohol per non-specific portion size was calculated. For beer and cider, which are combined on the FFQ (except in UKWCS) but not in the diet diary data, we used the average proportion of total beer and cider intake that was beer alone and that was cider alone to estimate an average amount of alcohol per half pint of beer and cider combined. A similar procedure was followed for fortified wine and liqueurs, which were combined on the FFQ (except in Whitehall II) but not in the diet diary data. The above calculations were performed separately by study using information summarized in the last two columns of Table 2B. For each beverage type, the calibrated FFQ measurement was calculated by multiplying the alcohol amount per calibrated portion size by the frequency reported in the FFQ. Total alcohol intake was calculated as the sum of alcohol from all beverage types.

Statistical analysis

Associations between alcohol intake and breast cancer were investigated first using FFQs and diet diaries separately, followed by the calibrated FFQ measurements, using the models described below.

We also propose a combined measure of alcohol intake using calibrated FFQ and diet diary measurements, devised to take advantage of both measurements, including that FFQs are likely to capture never-consumers more reliably. Figure 1 shows scatter plots of FFQ and calibrated FFQ measurements against diet diary measurements, showing no evidence of systematic differences between the latter pair. To obtain the combined measurement, individuals with a measurement of zero alcohol intake on both the FFQ and the diet diary were assigned a combined measurement of zero (476 individuals). Those with a measurement of zero on the diary but greater than zero on the FFQ were assigned their calibrated FFQ measurement (333 individuals), and vice versa (135 individuals). Those with non-zero measurements from both the FFQ and the diary were assigned the mean of their calibrated FFQ and diary measurements (1617 individuals). This is referred to as combined measurement 1.

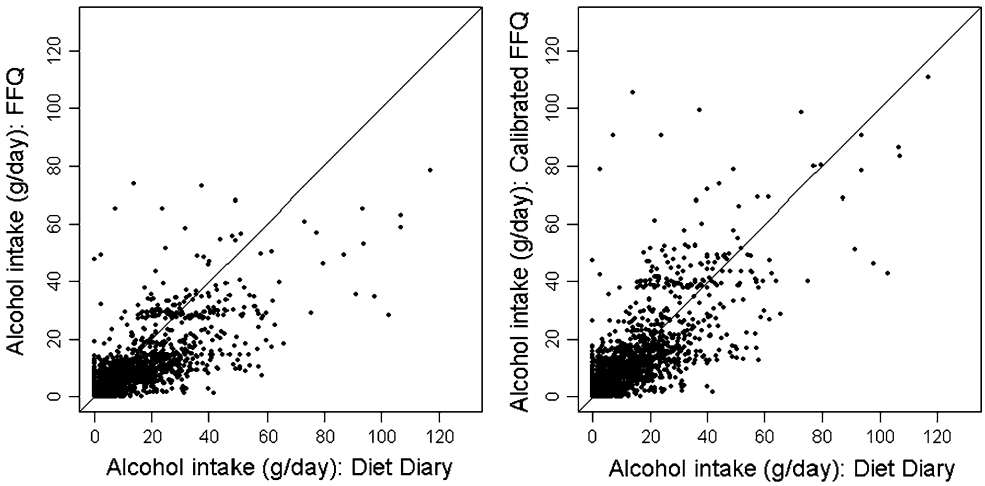

Fig. 1 Scatter plots of FFQ and calibrated FFQ measurements against diet diary measurements of alcohol intake

Repeated 7-day diary measurements of alcohol intake were available for 281 women (62 cases, 219 controls) in EPIC-Norfolk from a second time point. This enabled us to use measurement error modelling to correct for bias in OR estimates found using diet diary measurements from one time point. We fitted the 'never and episodic consumers model' [32] to the diet diary data with adjustment using FFQ measurements. This model takes into account the special issues associated with zero measurements in diet diary data. For the covariate-adjusted diet-disease model described below, the variables used in the multivariable model were also adjusted for in the measurement error model. This procedure resulted in an estimate of 'expected true intake' for each individual, conditional on both diet diary and FFQ data and, in the case of the multivariable model, also on individual characteristics. Using regression calibration [33], which is well established technique for measurement error correction, the expected true intake values were used in the regression models described below to obtain corrected estimates of association. The expected true intake is in essence a combined measure based on the observed dietary data and we refer to it as combined measure 2. Note that because this method gives an expected value for true intake it does not assign values of zero.

The data across all studies was pooled and conditional logistic regression models were used to estimate odds ratios (ORs) and 95 % confidence intervals (CI) for breast cancer risk according to alcohol intake, with and without adjustment for potential confounders. This corresponds to a fixed-effect meta-analysis. Heterogeneity in the association across study centres was assessed using the I^2 statistic [34]. We present ORs per 10 g/day increase in alcohol intake, approximately equivalent to 1 Unit, and compare ORs found using diet diary, FFQ, calibrated FFQ and the two combined measurements. ORs within categories of intake are also presented, except for combined measurement 2, since the method of regression calibration does not extend to allow categorization of the expected value. Tests for the difference between FFQ and diet diary estimates were performed by estimating the standard error of the difference between log OR estimates from the two different regressions using bootstrapping. Non-linearity in the association was investigated by including squared terms for the alcohol measurement in the regression.

A multivariable model adjusted for exact age, parity, height, weight, HRT use at baseline, physical activity, menopausal status, smoking status, education level, and energy and folate intake measured using the diet diary. Multiple imputation was used to handle missingness in adjustment variables using 10 imputed data sets (12 % of individuals were missing data in one or more of the above variables). Family history of breast cancer was missing completely in EPIC-Oxford and Whitehall II, and social class was missing completely in EPIC-Oxford. These variables were adjusted for in a sensitivity analysis. Wald tests were used to test for interactions of alcohol intake with HRT use, menopausal status and folate intake.

All statistical tests were two sided, and all statistical analyses were performed using Stata version 10 (Stata Corporation, College Station, TX, USA), except the never and episodic consumers model which was fitted in R. Multiple imputation was performed using the 'ice' [35] and 'mim' [36] packages in Stata.

Results

Measurements of alcohol intake

Table 3 summarizes alcohol intake measures obtained using diet diary, FFQ, calibrated FFQ and the combined

Table 3 Summary of alcohol intake measured using diet diary, FFQ, calibrated FFQ, and combined measurements, among all individuals, by case–control status, and by study centre

	% Reporting 0 intake			Mean (SD) alcohol intake in g/day				
	Diet diary	FFQ	Combined measurement 1	Diary	FFQ	Calibrated FFQ	Combined measurement 1	Combined measurement 2
All individuals								
Total alcohol	32	24	19	9.3 (13.2)	6.3 (9.3)	8.5 (12.6)	9.2 (12.1)	8.5 (11.4)
Wine	51	31	28	5.7 (9.7)	4.0 (7.2)	5.4 (9.8)	5.9 (9.1)	–
Beer/lager/cider	79	73	67	0.96 (3.4)	0.77 (2.9)	0.72 (2.7)	0.98 (2.9)	–
Spirits	77	64	61	1.7 (5.4)	0.91 (2.7)	1.6 (4.6)	1.9 (4.9)	–
Fortified wine/liqueurs	75	65	59	0.91 (2.4)	0.61 (1.7)	0.82 (2.3)	1.0 (2.3)	–
Controls: total alcohol	33	25	20	8.9 (13.0)	5.9 (8.9)	8.0 (12.0)	8.7 (11.7)	8.1 (11.2)
Cases: total alcohol	27	20	16	10.5 (13.7)	7.4 (10.3)	10.1 (14.1)	10.5 (13.0)	9.7 (12.0)
Study centre: total alcohol								
EPIC-Norfolk	35	26	21	8.2 (12.2)	5.7 (8.9)	7.9 (12.2)	8.3 (11.5)	7.2 (10.7)
UKWCS	32	19	16	8.6 (10.5)	6.6 (8.4)	6.7 (8.5)	8.1 (8.8)	9.4 (9.8)
EPIC-Oxford	25	21	16	11.0 (13.6)	7.4 (10.0)	9.9 (13.5)	10.6 (12.4)	10.6 (11.7)
Whitehall II	25	20	14	13.0 (17.6)	7.8 (10.6)	11.1 (15.0)	12.3 (15.6)	11.8 (14.1)

measurements. The number of women assigned zero intake was higher on the diet diary than the FFQ, which, as discussed in the introduction, was expected because of the short term nature of this instrument. Combined measurement 1 naturally gave the lowest number of zeros. Both mean alcohol intake and the proportion of individuals assigned non-zero consumption were higher among cases than controls. Intake differed somewhat across the case–control samples from the four study centres. The EPIC-Norfolk sample contained the highest proportion of individuals assigned zero intake for both FFQ and diet diary, and Whitehall II the lowest.

Participant characteristics and alcohol intake

Table 4 presents participant characteristics in categories of alcohol intake according to combined measurement 1. We chose to use combined measurement 1 here since it is a simple and intuitive combination of the two available measurements. As noted earlier, combined measurement 2 does not assign any values of zero intake. Individuals assigned zero intake using combined measurement 1 tended to weight more, were less physically active, had lower level of education, were of lower social class, and were more likely to be postmenopausal but less likely to be users of HRT. Heavier drinkers were younger, taller, and more likely to have no children and to be smokers. Energy intake increased with higher alcohol consumption, while there was no difference in folate intake across categories of alcohol intake. Family history of breast cancer was not associated with alcohol intake.

Alcohol intake and breast cancer

Figure 2 shows adjusted OR estimates within studies using combined measurement 1: there is no evidence of heterogeneity between studies ($I^2 = 0.0$ %). All studies apart from UKWCS showed a positive association between alcohol intake and breast cancer risk. Because of its size UKWCS sample did not make a large contribution to the pooled estimate. All subsequent results were based on a pooled, i.e., fixed-effect, analysis. Table 5 shows OR estimates per 10 g/day increase in alcohol intake and within categories of intake. The OR per 10 g/day increase in total alcohol intake found using FFQ measurements (unadjusted: OR 1.15 (95 % CI 1.05,1.26), adjusted: 1.13 (95 % CI 1.02,1.24)) was higher than that found using diet diary measurements (unadjusted: 1.07 (95 % CI 1.00,1.15), adjusted: 1.05 (95 % CI 0.98,1.13)).

Very similar estimates were found using the calibrated FFQ (adjusted OR 1.09 (95 % CI 1.02,1.17)), combined measurement 1 (adjusted OR 1.09 (95 % CI 1.01,1.17)) and combined measurement 2 (adjusted OR 1.09 (95 % CI 0.99,1.20)). There was a significant difference between the OR estimates found using FFQ and diet diary measurements (p value 0.028) and between calibrated FFQ and diet diary estimates (p value 0.047).

Additional adjustment for family history and social class had little effect on the results, and including a quadratic term for alcohol intake in the logistic regression provided no evidence of a non-linear association with breast cancer risk (results not shown).

Table 4 Distribution of participant characteristics by categories of alcohol intake using combined measurement 1

	Alcohol intake (g/day)							p value[a]	Number (%) missing
	0	>0 to ≤5	>5 to ≤10	>10 to ≤15	>15 to ≤20	>20 to ≤30	>30		
Number of cases/controls	102/374	203/626	115/331	80/212	41/127	59/116	56/119	0.018	0
Alcohol intake (g/day)	0	2.3 (1.3)	7.3 (1.4)	12.4 (1.4)	17.4 (1.5)	24.0 (2.9)	43.2 (14.0)	–	0
Age (years)	60.0 (9.1)	57.5 (9.1)	56.2 (9.3)	56.1 (9.5)	54.9 (8.8)	55.1 (9.2)	53.2 (8.7)	<0.001	0
Height (m)	161.0 (6.5)	161.3 (6.5)	161.9 (6.7)	162.6 (6.3)	162.9 (6.0)	163.1 (6.2)	163.7 (6.0)	<0.001	13 (0.5%)
Weight (kg)	68.6 (12.8)	68.2 (12.6)	66.5 (11.2)	66.2 (11.2)	65.5 (10.1)	66.6 (11.3)	68.0 (12.4)	0.003	27 (1.1%)
HRT use (%)								0.001	52 (2.0%)
Yes	11.8	19.7	17.6	24.6	20.2	20.6	19.5		
Physical activity (%)								0.001	101 (3.9%)
High[d]	32.0	35.8	44.1	41.9	44.2	44.9	41.2		
Parity (%)								0.014	11 (0.4%)
0	19.4	18.5	19.5	18.5	21.6	20.6	32.2		
1	12.7	13.2	12.9	11.6	12.0	18.3	11.5		
2	37.1	42.6	39.1	42.1	40.1	32.6	38.5		
3+	30.8	25.7	28.5	27.7	26.4	28.6	17.8		
Menopausal status (%)								<0.001	25 (1.0%)
Pre	10.4	14.3	21.0	22.3	21.6	24.3	30.3		
Peri	8.9	12.3	11.2	10.0	15.6	15.0	18.3		
Post	80.7	73.4	67.9	67.7	62.9	60.7	51.4		
Smoking status (%)								<0.001	30 (1.2%)
Never	67.1	65.6	53.5	60.3	56.9	46.5	34.7		
Former	23.3	25.2	35.6	31.4	32.3	43.6	48.0		
Current	9.6	9.2	10.9	8.3	10.8	9.9	17.3		
Education level (%)								<0.001	139 (5.4%)
High[e]	32.5	39.7	47.8	55.9	55.4	63.7	62.7		
Social class (%)								<0.001	434 (17.0%)[b]
Non-manual	56.6	63.1	71.3	78.7	81.3	81.6	85.7		
Family history of breast cancer (%)								0.211	720 (28.1%)[c]
Yes	7.1	6.6	7.9	6.8	5.3	13.4	9.9		
Total energy intake (kcal/day)	1677 (420)	1712 (382)	1744 (390)	1798 (365)	1855 (385)	1865 (369)	1976 (405)	<0.001	0
Folate intake (μg/day)	256 (82)	257 (77)	254 (74)	259 (73)	252 (76)	258 (75)	255 (79)	0.966	0

Results are mean (standard deviation) except where otherwise indicated

[a] For categorical variables χ^2 tests were used to test whether the distribution of individuals across categories differed significantly across categories of alcohol intake. For continuous variables the p value is from a one-way analysis of variance

[b] Social class is missing in EPIC-Oxford

[c] Family history is missing in EPIC-Oxford and Whitehall II

[d] High physical activity includes those classified as being 'moderately activ'' or 'active'. The remainder of individuals were classified as 'inactive' or 'moderately inactive'

[e] High education level includes individuals who reported education at least up to A-level or equivalent (up to age 17).

Subgroup analyses

Table 6 shows OR estimates within subgroups according to HRT use, menopausal status and folate intake. There was a significant interaction between alcohol intake and HRT use with the estimated OR per 10 g/day increase in alcohol intake being considerably higher and statistically significant among HRT users. Using combined measurement 1 the OR was 1.43 (95 % CI 1.05,1.93) among HRT users and 1.06 (95 % CI 0.97,1.16) among non-users. Combined measurement 2 gave an adjusted OR of 1.59 (1.10–2.30) among HRT users and 1.05 (0.93–1.19) among non-users. Exclusion of the EPIC-Oxford study, in which all individuals in the case–control sample were non-users

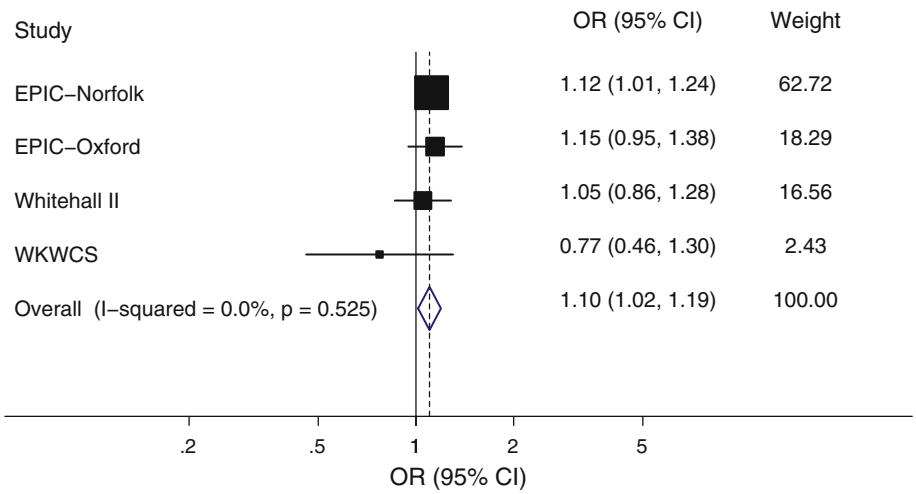

Fig. 2 Adjusted odds ratio estimates per 10 g/day increase in alcohol intake using combined measurement 1 within studies and the pooled estimate from a fixed-effect meta analysis

Table 5 Odds ratio (OR) estimates (95% confidence interval) per 10 g/day increase in total alcohol intake and in categories of total alcohol intake obtained using diet diary, FFQ, calibrated FFQ, and combined measurements

	Diet diary	FFQ	Calibrated FFQ	Combined measurement 1	Combined measurement 2[b]
Unadjusted					
Per 10 g/day	1.07 (1.00–1.15)	1.15 (1.05–1.26)	1.12 (1.05–1.20)	1.11 (1.03–1.19)	1.10 (1.02–1.19)
Intake category (g/day)					
0	0.85 (0.66–1.11)	0.84 (0.65–1.08)	0.85 (0.65–1.10)	0.84 (0.63–1.11)	–
>0 to ≤5	Ref	Ref	Ref	Ref	–
>5 to ≤10	1.15 (0.85–157)	1.15 (0.89–1.49)	1.23 (0.93–1.61)	1.09 (0.83–1.43)	–
>10 to ≤15	1.11 (0.78–1.60)	1.10 (0.79–1.52)	0.88 (0.63–1.22)	1.17 (0.86–1.61)	–
>15 to ≤20	1.03 (0.69–1.53)	2.10 (1.27–3.47)	1.14 (0.78–1.67)	0.96 (0.65–1.43)	–
>20 to ≤ 30	0.98 (0.68–1.42)	1.23 (0.77–1.96)	2.05 (1.33–3.16)	1.45 (1.01–2.09)	–
>30	1.51 (1.04–2.18)	1.43 (0.87–2.36)	1.40 (0.96–2.03)	1.41 (0.97–2.03)	–
Adjusted[a]					
Per 10 g/day	1.05 (0.98–1.13)	1.13 (1.02–1.24)	1.10 (1.03–1.18)	1.09 (1.01–1.18)	1.09 (0.99–1.20)
Intake category (g/day)					
0	0.87 (0.66–1.13)	0.84 (0.65–1.08)	0.85 (0.65–1.12)	0.85 (0.64–1.13)	–
>0 to ≤ 5	Ref	Ref	Ref	Ref	–
>5 to ≤ 10	1.20 (0.88–1.63)	1.16 (0.89–1.509)	1.25 (0.95–1.66)	1.12 (0.85–1.48)	–
>10 to ≤15	1.08 (0.75–1.57)	1.09 (0.78–1.52)	0.89 (0.63–1.25)	1.17 (0.85–1.61)	–
>15 to ≤20	1.04 (0.69–1.55)	2.02 (1.21–3.37)	1.12 (0.76–1.66)	0.94 (0.62–1.42)	–
>20 to ≤30	0.95 (0.65–1.39)	1.16 (0.92–1.15)	1.99 (1.27–3.12)	1.44 (0.99–2.10)	–
>30	1.41 (0.96–2.08)	1.31 (079–2.19)	1.32 (0.89–1.95)	1.31 (0.89–1.94)	–

[a] Adjusted for exact age, parity (0, 1, 2, 3+), height (m), weight (kg), HRT use at date of diary completion (yes/no), physical activity (inactive, moderately inactive, moderately active, active), total energy intake (kcal/day), folate intake (μg/day), menopausal status (pre, peri, post), smoking (never, former, current), education level (no qualifications, O-level or equivalent (up to age 15), A-level or equivalent (up to age 17), degree level or equivalent), using multiple imputation

[b] It is not appropriate to estimate ORs within groups using combined measurement 2

of HRT, had little effect on these results. There was no statistically significant difference in the alcohol–breast cancer association by menopausal status or by diet sources of folate intake.

Discussion

In this study we have been able, for the first time, to compare estimates of the alcohol–breast cancer association

Table 6 Adjusted odds ratios (95 % confidence intervals) for a 10 g/day in alcohol intake measured using diet diary, FFQ, calibrated FFQ, and combined measurements in subgroups according to HRT use, menopausal status, and folate intake, all at baseline

Subgroup	Number of cases/controls	Diet diary	FFQ	Calibrated FFQ	Combined measurement 1	Combined measurement 2
HRT non-users	532/1565	1.03 (0.94–1.12)	1.10 (0.97–1.24)	1.08 (0.99–1.18)	1.06 (0.97–1.17)	1.05 (0.93–1.19)
HRT users	118/358	1.43 (1.06–1.93)	1.46 (0.97–2.21)	1.35 (1.01–1.81)	1.45 (1.06–1.99)	1.59 (1.10–2.30)
p value		0.06	0.03	0.02	0.02	0.04
Pre-menopausal	110/360	1.00 (0.85–1.18)	1.09 (0.85–1.39)	1.07 (0.90–1.29)	1.04 (0.87–1.24)	1.00 (0.80–1.26)
Peri-menopausal	113/193	1.12 (0.82–1.53)	0.98 (0.70–1.36)	1.05 (0.78–1.40)	0.97 (0.65–1.45)	0.97 (0.65–1.45)
Post-menopausal	423/1390	1.08 (0.97–1.19)	1.16 (1.01–1.33)	1.13 (1.02–1.24)	1.12 (1.01–1.25)	1.13 (1.00–1.29)
p value		0.19	0.34	0.30	0.18	0.26
Tertile 2 of folate intake (≥217.36 to <277.45 g/day)	200/654	1.02 (0.83–1.26)	1.05 (0.80–1.37)	1.06 (0.86–1.29)	1.02 (0.82–1.27)	0.93 (0.71–1.20)
Tertile 2 of folate intake (≥217.36 to <277.45 g/day)	230/624	1.05 (0.87–1.27)	1.19 (0.96–1.48)	1.17 (0.99–1.37)	1.14 (0.94–1.37)	1.10 (0.88–1.38)
Tertile 3 of folate intake (≥277.45 to <744.71 g/day)	226/627	1.00 (0.83–1.21)	1.16 (0.86–1.57)	1.12 (0.84–1.42)	1.07 (0.85–1.34)	1.13 (0.88–1.46)
p value		0.17	0.17	0.13	0.14	0.16

Adjusted for exact age, parity (0, 1, 2, 3+), height (m), weight (kg), HRT use at date of diary completion (yes/no), physical activity (inactive, moderately inactive, moderately active, active), total energy intake (kcal/day), folate intake (μg/day), menopausal status (pre, peri, post), smoking (never, former, current), education level (no qualifications, O-level or equivalent (up to age 15), A-level or equivalent (up to age 17), degree level or equivalent), using multiple imputation. *p*-values are from Wald tests

using both diet diary and FFQ measurements of alcohol intake. We investigated the association between prospectively measured alcohol intake and breast cancer in a matched case–control study sampled within four UK cohorts.

Adjusted OR estimates per 10 g/day of alcohol intake were significantly higher using FFQ compared with diet diary measurements (ORs 1.13 and 1.05). The difference is partly due to lower portion sizes being used to obtain FFQ measurements. Portion sizes used for the diet diary calculations were considered to be more appropriate for intake recorded in the 1990s, as in this study. However, calibration of FFQ measurements, to place them on the same scale as diet diary measurements, gave an adjusted OR (1.10) only a little closer to that found using the diet diary. This suggests that portion sizes do not account for most of the difference between estimates obtained using FFQs and diet diaries. With respect to measuring habitual intake, a major source of error in diet diary measurements is the excess zeros which arise due to episodic consumers, and this may account for a large portion of the apparent attenuation in the diet diary estimates. Both instruments are subject to error from a range of other sources [14]. FFQs are subject specifically to error due to difficulty of recall, lack of information on portion sizes, and omission of food items, though this may not be large problem for alcoholic beverages. Sources of error in short term diet diary measurements include variability in dietary intake over time and lack of detail being provided. Both types of measurement suffer error from selective and mis-reporting. Alcohol may be a particular item which is systematically under-reported [37].

We considered two ways of combining the FFQ and diet diary measurements to make best use of the available data and to go some way towards correcting for measurement error. A particular challenge was how to treat zero measurements. Combined measurement 1 took the average of diet diary and calibrated FFQ measurements, with special treatment of zeros. Combined measurement 2 was the expected true intake conditional on the diet diary and FFQ, calculated by fitting a measurement error model to the data, which required use of a repeated diet diary measurement available in a subset of the EPIC-Norfolk sample. The combined measurements gave adjusted ORs very close to that obtained using the calibrated FFQ (1.11 and 1.09).

Here we discuss what our findings tell us about which instrument or combination of instruments may give the 'best', that is most unbiased, estimate of the association between alcohol intake and breast cancer, or other outcomes. In the absence of a recovery biomarker for alcohol intake, however, it is not possible to draw firm conclusions. Use of a diet diary from one time point appears to clearly result in attenuated OR estimates due to episodic consumers. Correction for error in the diet diary using a measurement error model which accounts both for excess zeros and random error in non-zero measurements gives

apparently deattenuated results, which is expected [32]. It is important to note that the model used to obtain combined measurement 2 assumes random error in non-zero diary measurements. This assumption has been shown to be invalid in studies of nutrients for which there is a recovery biomarker [16–18], and is thought to typically result in a partial but not complete correction for measurement error. The fitting of the never and episodic consumers measurement error model to obtain combined measurement 2 also makes the assumption that an individual who reports non-zero intake on the FFQ is not a never-consumer, which seems reasonable, but it does not assume that individuals assigned zero intake on the FFQ are necessarily never-consumers. Combined measurement 1 is a simple and intuitive way of combining both measurements, but has the disadvantage of being ad hoc. In this study we found that using the calibrated FFQ measurement alone, and combined measurements 1 and 2 gave similar OR estimates. However, it is not possible to ascertain whether this finding should persist across other studies. What is clear from this study is that investigators should take care to assign appropriate portion sizes for use in programs designed to obtain both FFQ and diet diary measurements and be aware that too-low portion sizes can result in spuriously high associations. Obtaining more detailed information about typical portion sizes, for example from weighed food records, seems to be important if more firm conclusions about the effects of alcohol on disease risk are to be made. However, this may not be possible retrospectively because typical portion sizes for alcohol may have changed over time.

Strengths of our study include the use of a common program (DINER) to obtain most diet diary measurements, data on a large number of potential confounders, and the availability of repeated diet diary measurements. Our study also has some limitations. Potential confounders were assessed at baseline and it was not possible to investigate the effect of potential effect modifiers closer to diagnosis. Alcohol intake was also assessed only at one time point. We were unable to investigate whether the association between alcohol and breast cancer differed according to tumour subtypes and hormone receptor status [6, 9, 10, 12, 38] and there was insufficient data to investigate the effect of different alcohol beverages [8, 39, 40].

Previous studies have been based on questionnaire measurements of alcohol intake. The Million Women Study recently found a relative risk of 1.12 (95 % CI 1.09, 1.15) for a 10 g/day increase in alcohol intake based on 22,000 cases among drinkers [2]. Meta analyses have found combined OR or relative risk estimates per 10 g/day increase in alcohol intake of 1.09 (95 % CI 1.04, 1.13) [8], 1.071 (95 % CI 1.055, 1.087) [3], and 1.11 (95 % CI 1.05,1.15) [5]. A meta-analysis of data from 10 countries in EPIC-Europe found a much smaller overall estimated incidence rate ratio of 1.03 (95 % CI 1.01, 1.05) per 10 g/day increase in alcohol intake, also using questionnaire-based data [41]. Some studies have suggested that the association between alcohol intake and breast cancer risk may be modified by HRT use [42]; menopausal status [43, 44]; and folate intake [45–47]. In our results the association was significantly larger among women who reported using HRT at baseline compared with non users. However, neither the Million Women Study [2] nor the EPIC-Europe study [41] found evidence of any interaction by HRT use and further studies using information about use over time are encouraged. We found no evidence of differences in the association by dietary folate intake or menopausal status.

In summary, our results indicate an increased risk of breast cancer even for a small increase in daily alcohol intake, with an estimated 10 % increase per 10 g/day increase in alcohol intake. This is broadly in agreement with results from previous studies. Our study provides evidence that the association is likely to be underestimated using a diet diary measurement from one time point.If using only one measurement, a FFQ would be preferred over a diet diary on the basis of these results, provided the FFQ measurements are based on appropriate portion sizes. Further investigations are needed to investigate what, if anything, a combination of both measurements, or use of repeated two or more diet diary measurements, can offer over a single FFQ measurement. However, common sense suggests that two measurements should be better than one in general, provided they are appropriately combined.

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